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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
O'HARA, EILEEN B	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,191	GODDARD ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006 and 06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-63,69 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-63,69 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 7, 2006 has been entered. Applicant's Supplemental Amendment filed Sept. 9, 2006 has also been entered.

Claims

2. Claims 58-63, 69 and 70 are pending in the instant application.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 and 112, first paragraphs read as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 58-63, 69 and 70 remain rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed June 2, 2004, at pages 5-9, March 16, 2005 at pages 3-10, Sept. 20, 2005, Feb. 8, 2006 and below.

Claims 58-63, 69 and 70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' arguments (pages 5-23, Paper filed July 7, 2006 and pages 2-4, Paper filed Sept. 6, 2006) have been fully considered but are not fond to be persuasive for the following reasons.

Applicant relies on the gene amplification data for the gene encoding PRO213-1 polypeptide for patentable utility of the PRO213-1 polypeptide. The Examiner does not dispute that the nucleic acid is amplified in a number of cancers and that this provides a specific and substantial utility for the nucleic acids. The issue is whether or not amplified DNA correlates with increased mRNA, and whether or not increased mRNA levels correlates with increased protein levels. The art supports this position by establishing that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Pennica et al., and Gygi et al. of record.

Applicants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration, and accordingly, submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that a person of ordinary skill in the pertinent art would doubt the truth of the statement of utility, and that the standard is not absolute certainty. Applicants submit that the law requires only that one skilled in the art should accept that such a correlation is more likely than not to

exist. Applicants submit that the references cited by the PTO are either irrelevant, not contrary to Applicants' arguments, or actually offer support for Applicants' position. Applicants submit that the teachings of Pennica et al. are specific to WISP genes, and say nothing about the correlation of gene amplification and protein expression in general, and the Gygi et al. supports Applicants position that there is a positive correlation between the overexpression of mRNA and protein.

Applicants on pages 7-9 of the response submit that the authors of Lian et al. themselves admit that there are a number of problems with the data presented in this reference, such as the insensitivity of Coomassie dye stain, and the low level of proteins examined (50) compared to the approximately 7000 genes for which mRNA levels were measured. Applicants submit on page 9 that only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change in protein level an one does not.

These arguments have been considered but are not persuasive. When reading many if not most of papers in this field, the authors generally readily admit to limitations in the methods used. But these papers are published in peer reviewed journals and are therefore considered relevant. Additionally, even if only two genes meet the authors' criteria for differentially expressed mRNA level and one shows a corresponding change in protein level and one does not, one of skill in the art would determine that it is not predictable that a change in mRNA would lead to a corresponding change in protein.

Applicants on pages 9-10 discuss Fessler et al., who looked at proteins that were up or down-regulated and then looked at corresponding mRNA levels, and submit that in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA

corresponds to the change in the level of the protein. Applicants argue that changes in protein levels when mRNA levels are unchanged are not relevant, and that Fessler's results are consistent with Applicants' assertion that a change in mRNA level for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Applicants' arguments have been fully considered but are not deemed persuasive. Fessler is evidence that there is a poor correlation between changes in levels of protein and corresponding changes in levels of mRNA, as the authors themselves state.

Applicant discuss the Chen et al. reference, and reiterate that no attempt was made to compare expression levels in normal versus tumor samples, and that the authors concede that they had too few normal samples for meaningful analysis (page 310, col. 2). Applicant asserts that as a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples, and the Chen paper does not address the issue of whether increased mRNA levels in the tumour samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumour tissue versus normal tissue.

This has been considered but not found persuasive. The section in Chen referred to did not refer to the entire sample, but addressed determining whether the 21 genes showing a significant correlation between the protein and mRNA expression among all samples demonstrate changes in this relationship during tumour progression, and the correlations were examined separately for stage I (n=57) and stage III (n=9) lung adenocarcinomas. The number of non-neoplastic lung samples (n=9) was insufficient for a separate correlation analysis of this

group. Regarding the argument that Chen et al. did not examine the correlation between increases in mRNA and protein expression in tumor tissue as compared to normal tissue, and therefore Chen et al. is nor applicable to the application at issue, Chen et al. is support for the assertion that transcript levels do not necessarily correlate with protein levels.

Applicants on page 11 of the response discusses Anderson et al., and submit that this reference looked at levels of mRNA in the same, non-disease state across different genes, and not changes in mRNA levels for a single gene, and Anderson et al. is not inconsistent with or contradictory to the utility of the instant claims and offers no support for the PRO's rejection of Applicants' asserted utility.

This has been considered but not found persuasive. Anderson et al. is support for the assertion that transcript levels do not necessarily correlate with protein levels.

Nagaraja et al. (Oncogene, 25:2328-2338, 2006), provide data comparing transcript and protein levels between normal of cancer tissue. Nagaraja et al. characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly,

Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO213-1. The specification simply discloses a static measurement

of PRO213-1 mRNA in colon tumor as compared to a universal control. There are no teachings in the specification as to the differential expression of PRO213-1 mRNA in the progression of colon cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO213-1 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351-352). teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286, especially pg 283). King et al. (JAMA, Nov. 2001, Vol. 286, No. 18, pages 2280-2288) disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct

analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Madoz-Gurpide et al., Adv. Exp. Med. Biol., Vol. 532:51-58, 2003, disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph).

Given the asserted increase in PRO213-1 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO213-1 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and, "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO213-1 polypeptides have utility in the fields of cancer diagnostics is not substantial.

Response to Applicants' Argument of Sept. 6, 2006:

Declarations by Dr. Polakis and Dr. Randy Scott:

The Declarations filed by Dr. Polakis and Dr. Randy Scott have been fully considered, but are not effective to overcome the rejection of claims 58-63, 69 and 70 made under 35 U.S.C. 101/112, first paragraph.

Applicant refers to a second declaration of Dr. Polakis (Polakis II), submitted with the response (filed 07 July 2006). Applicant argues that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 12 July 2006 is insufficient to overcome the rejection of claims 58-63, 69 and 70 based upon 35 U.S.C. §101 and §112, first paragraph, for the following reasons. Specifically, data for PRO213-1 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table compare to PRO213-1, or if the results presented in the table were determined by the same methodology as presented in Example 30 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., Microarray, Northern blot, quantitative PCR? Was the "universal normal control" used or were matched tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Applicant further submits a Declaration by Dr. Randy Scott. Dr. Scott explains that DNA microarray technology is widely used and has an impressive commercial success. Dr. Scott states that although there are some exceptions on an individual gene

basis, it has been a consensus in the scientific community that elevated mRNA levels are good predicator of increased abundance of the corresponding translated proteins in a particular tissue. Dr. Scott concludes that diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression level. Applicant submits that Dr. Scott who has unparalleled experience with both the microarray technique and its industrial and clinical application, supports Applicant's position that this technique is not only mature, reliable and well accepted in the art, but also has been extensively used in drug development and in diagnosis of various diseases and produced enormous commercial success.

Dr. Scott's Declaration as well as Applicant's argument pertaining it have been fully considered, but are not deemed persuasive.

The usefulness of the micrroarray technique and its commercial success are acknowledged. However, the issue at hand is whether the correlation between mRNA and protein levels is predictable. Therefore, although the instant specification discloses that the PRO213-1 mRNA is expressed in colon and lung tumor, there is no disclosure as to how high is it expressed and whether it is correlated with developing these tumors. Moreover, the commercial success of the micrroarray technique is immaterial to the instant invention, because evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is irrelevant to utility and enablement. Finally, Applicant cites numerous references that allegedly show a correlation between mRNA and protein level and the Examiner cites numerous

references that allegedly show that there are instances where there is no correlation between mRNA levels and the protein levels. Therefore, it is apparent that the state of the art is such that correlation between mRNA levels and proteins levels is unpredictable and should be determined on a case by case manner. Thus, data is needed showing there is a correlation between PRO213-1 mRNA levels and the level of the PRO213-1 polypeptide, so that the level of reproducibility or the level of reliability of the results can be independently verified. Since the specification does not disclose any data, it cannot be said that the microarray assay consistently and reliably results in high correlation between PRO213-1 mRNA levels and protein expression levels in colon and lung tumor samples.

4. Claims 58-62, 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth at pp. 9-10 of the Office Action mailed 02 February 2004, pages 11-13 of the Office Action mailed 16 March 2005 and pages 17-19 of the Office Action mailed Feb. 8, 2006. The specification discloses a single amino acid sequence for PRO213-1, SEQ ID NO: 506. There is a utility and enablement issue regarding whether or not the nucleic acid encoding PRO213-1 is amplified in lung tumors (see rejections under 35 U.S.C. §§ 101 and 112, first paragraph, above). Furthermore, the specification does not

disclosure any variants of SEQ ID NO: 506, nor whether such sequences are amplified in lung tumors.

Applicant's arguments (pp. 23-26, remarks submitted July 7, 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant urges that such provides basis for the claimed genus of native polypeptide sequences with at least 80-99% sequence identity to SEQ ID NO: 506 which are functionally defined as being encoded by a nucleic acid that is amplified in lung or colon tumors. Applicant points to the specification's disclosure of methods for the determination of percent identity, and assays for identification of nucleic acids and for the functional limitation in the claims. Applicant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the encoding nucleic acids are amplified in lung or colon tumors. This has been fully considered but is not found to be persuasive. The courts have specifically stated that if the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide, until the structure is disclosed, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, SEQ ID NO; 506 has been disclosed, but no variants thereof have been disclosed regardless of whether or not they are encoded by nucleic acids that are amplified in tumors.

Applicants submit that the present application is different from *Fiddes v. Baird.* In that a common structure features, such as sequence similarity, was not provided in the claimed genus, and in contrast, claims 58-62 clearly define both common structural features (sharing at least 80%-99% sequence identity) and functional limitations (being overexpressed in lung or colon tumor cells).

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous office actions. 80% identity to a described sequence is not a true structure. It is not disclosed which of the 80% amino acids are important for activity. Additionally, being overexpressed in tumors is not a functional property, but a characteristic.

It is believed that all pertinent arguments have been answered.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER